Asian Journal of Chemistry Vol. 17, No. 4 (2005), 2639–2643

Synthesis of the C-2 Functionalized 1,4-Dihydropyridines

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Unsymmetrical 1,4-dihydropyridine esters **4** and **5** were synthesized from the symmetrical precursor **1** through the intermediacy of 2-bromomethyl derivative **2**. Then reaction of isothiouronium salt **4** with electrophilic specie, methyl iodide, in the presence of base produced S-methylated derivative **6**. Reaction of the dibrominated derivative **3** with lithium salt of 1,3-dithiane led to the formation of dithio acetal derivative **7**.

Key Words: Hantzschesters, 1,4-Dihydropyridine, Calcium antagonists.

INTRODUCTION

1,4-Dihydropyridine derivatives (DHPs), a major class of calcium antagonists, are in clinical use to treat angina pectoris, hypertension or subarachnoid hemorrhage[1].

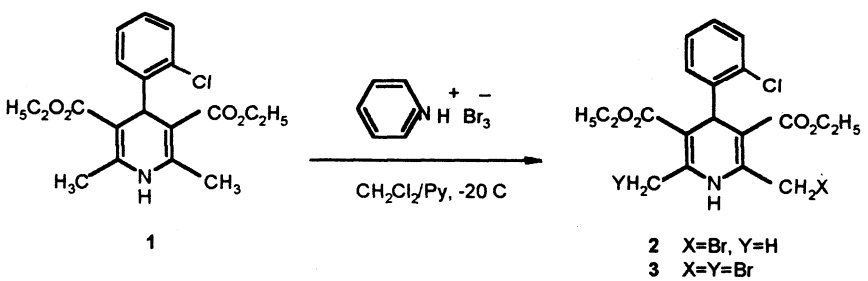
1,4-Dihydropyridine esters can be prepared by Hantzsch condensation reactions between various Knoevenagel-derived adducts and aminocrotonates or their β-keto ester precursors. Symmetrical 1,4-dihydropyridine esters are generally obtained in high yield using Hantzsch conditions. Unsymmetrical 1,4-dihydropyridine esters, however, are often more difficult to prepare due to the formation of all the possible isomeric Hantzsch condensation products[2]. As consequence of this, unsymmetrical Hantzsch products are usually obtained in significantly lower yield than their symmetrical counterparts and often require difficult and tedious chromatographic separation to effect their purification.

Routes to prepare unsymmetrical Hantzsch esters from simple symmetrical precursors have been developed to circumvent this problem. For example, a series of C-2 methyl substituted dihydropyridines have been obtained from symmetrical starting materials using Mannich type condensation routes[3]. Ultilization of anion chemistry at the C-2 methyl position of Hantzsch dihydropyridine esters has also been explored. Additionally, the C-2 methyl position of 1,4-dihydropyridine has been brominated with pyridinium bromide perbromide in CH_2Cl_2 or $CHCl_3$ to give α-bromomethyl intermediates which could be used for further chemical elaboration with various nucleophiles.

In this work, unsymmetrical 1,4-dihydropyridine esters **4** and **5** were synthesized from the symmetrical precursor **1** through the intermediacy of 2-bromomethyl derivative **2**. Then reaction of isothiouronium salt **4** with electrophilic specie, methyl iodide, in the presence of base produced S-methylated derivative **6**.

RESULTS AND DISCUSSION

Reaction of ethyl acetoacetate with 2-chloro benzaldehyde and ammonia in refluxing ethanol for 72 h, then recrystallization from EtOAc/Hexane gave **1** in 58% yield. Reaction of **1** with 1.1 equivalents of pyridinium bromide perbromide in dichloromethane/pyridine at –20°C for 45 min afforded the crude product **2** as a yellow gum; on the other hand, reaction of **1** with 2.1 equivalents of pyridinium bromide perbromide in dichloromethane at 0°C for 45 min gave the crude product **3** as a pale yellow solid **(Scheme-1).** The synthesis of mono brominated 1,4-dihydropyridine derivatives[4] in high yield was done by modifying the literature method[5–7]. Without further purification, the brominated adduct **2** was coupled with thiourea and 2-mercapto-4,6-dimethyl pyrimidine and **3** was coupled with 1,3-dithiane-Li at different conditions to give respectively mono- and di-substituted 1,4-dihydropyridine derivatives **4, 5, 7.**



1

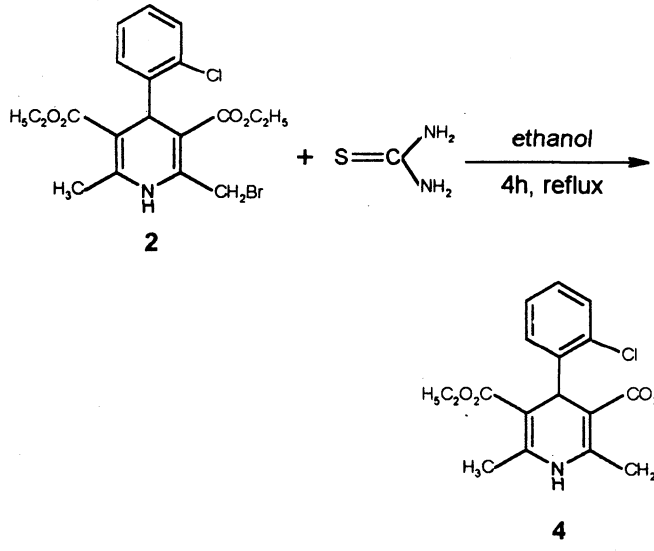
2 X=Br, Y=H
3 X=Y=Br

Scheme-1

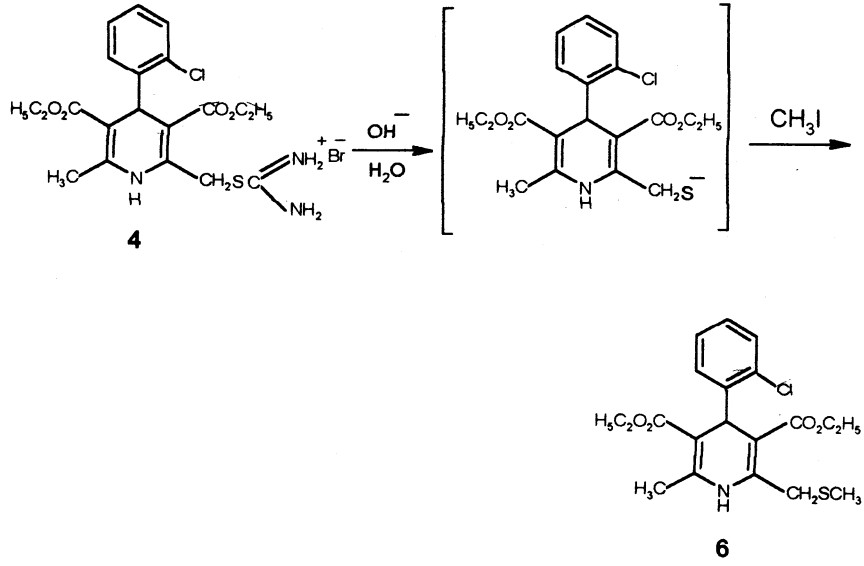
In spite of the low stability of **2,** which undergoes decomposition on heating to yield the expected lactone, it reacts with thiourea and 2-mercapto-4,6-dimethyl pyrimidine in refluxing ethanol to give respectively **4, 5** in high yield. In reaction of **2** with thiourea in refluxing ethanol for 5 h, evaporation of solvent and recrystallization from EtOAc/Hexane, isothiouronium salt **4** is formed **(Scheme-2).**

Since the isothioureido group may easily be introduced and isothiourea is easily transformed, the process is particularly flexible and adaptable to different synthetic procedures. Reaction of isothiournium salt **4** with electrophilic specie, methyl iodide, in the presence of base produces S-alkylated derivative **6 (Scheme-3).**

In the reaction of lithium salt of 1,3-dithiane with **2,** the products could not be separated and identified. This problem may be due to the relatively high acidity

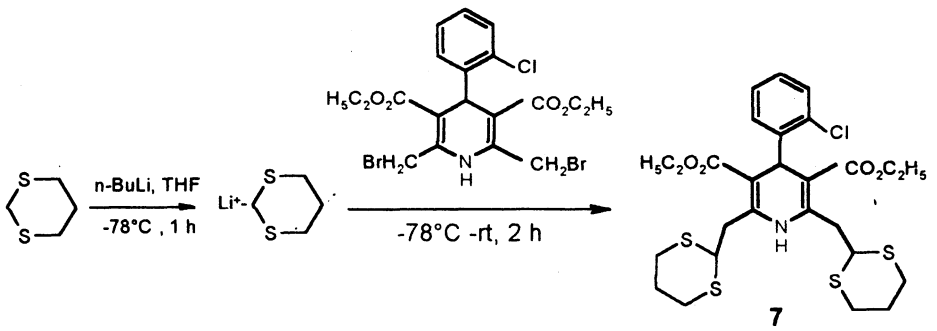


Scheme-2



Scheme-3

of C-6 methyl position; meanwhile we prepared the dibrominated derivative **3**; then reaction of lithium salt of 1,3-dithiane with **3** leads to the formation of dithio acetal derivative **7 (Scheme-4).**



Scheme-4

EXPERIMENTAL

THF was distilled from sodium/benzophenone under an argon atmoshpere. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker SP-400 spectrometer. IR spectra were recorded on a Bruker PS-15.

Preparation of S-[(6-methyl-3,5-dicarboethoxy-4-(2-chlorophenyl)1,4-dihydropyridin-2-yl)methyl]isothiouronium bromide, 4: A mixture of 2-bromomethyl-3,5-dicarboethoxy-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine[4] (obtained from 1.54 mmol of **1**), thiourea (0.13 g, 1.7 mmol) and ethanol (20 mL) was heated to reflux for 4 h and then evaporated. The residue was partitioned between CH_2Cl_2 and water and the organic layer washed with water, dried over Na_2SO_4 and evaporated. The residue was recrystallized in ethylacetate/hexane to give **4** (0.42 g, 53%) as yellow crystals. m.p. 165–167°C; IR (KBr, cm^{-1}) $\bar{\nu}$: 3350–2800 (br), 1720–1640 (s), 1515 (m), 1423, 1295, 1208, 1171, 1100; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.18 (t, J = 6.8 Hz, 3H), 1.22 (t, J = 6.8 Hz, 3H), 239 (s, 3H), 4.12 (m, 4H), 4.54 (d, J = 16 Hz, 1H), 4.73 (d, J = 16 Hz, 1H), 5.41 (s, 1H), 7.06 (dt, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.22 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.34 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H, ArH), 8.35 (s, 1H, NH), 8.75 (br s, 2H, NH), 9.12 (br s, 2H, NH) ppm.

2-[(4,6-Dimethyl pyrimidin-2-yl)thio]methyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine, 5: A mixture of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine (obtained from 2.74 mmol of **1**), 2-mercapto-4,6-dimethyl pyrimidine (0.42 g, 3.01 mmol) and ethanol (60 mL) was heated to reflux for 1.5 h and then evaporated. The residue was partitioned between CH_2Cl_2 (30 mL) and saturated Na_2CO_3 solution, and the organic layer washed with water, dried over Na_2SO_4 and evaporated. Recrystallization of crude product from 2-propanol furnished 2-[(4,6-dimethyl pyrimidin-2-yl)thio]methyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine (0.96 g, 70%) as yellow crystals. m.p. 150–151.8°C; IR (KBr, cm^{-1}) $\bar{\nu}$: 3441, 3050, 2979, 1686, 1640, 1532, 1285, 1046. ^1H NMR (400 MHz, $CDCl_3$) δ : 1.20 (m, 6H), 2.24 (s, 3H), 2.48 (s, 6H), 4.00–4.20 (m, 4H), 4.50 (AB quartet, J = 18 Hz, 2H), 5.41 (s, 1H), 6.80 (s, 1H), 7.03 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, ArH), 7.11 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.22 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.41 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H, ArH), 8.63 (s, 1H, NH) ppm.

Preparation of 2-(methyl thio)methyl-3,5-dicarboethoxy-6-methyl-4-(3-chlorophenyl)-1,4-dihydropyridine, 6: An aqueous solution of NaOH (32%, 1 mL) was added to a stirred solution of **4** (0.5 g, 0.99 mmol) and methyl iodide (0.34 g, 2.36 mmol) in ethanol/water (1 : 1, 20 mL), under an argon atmosphere. By addition of NaOH solution the yellow precipitate was formed immediately. After 30 min stirring at room temperature, the mixture was filtered. Recrystallization of the crude product from ethanol furnished compound **6** as pale yellow crystals in 60% yield. m.p. 118–119°C; IR (KBr, cm^{-1}) $\bar{\nu}$: 3318, 3092, 2976, 1688, 1498, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.21 (m, 6H), 2.06 (s, 3H), 2.34 (s, 3H), 3.91–4.14 (m, 6H), 5.46 (s, 1H), 6.75 (s, 1H, NH), 7.04 (dt, $J_1 = 7.2$ Hz, $J_2 = 0.8$ Hz, 1H, ArH), 7.12 (dt, $J_1 = 7.2$ Hz, $J_2 = 0.8$ Hz, 1H, ArH), 7.24 (m, 2H, ArH) ppm.

Preparation of 2,6-di [(1,3-dithian-2-yl)methyl]-3,5-dicarboethoxy-6-methyl-4-(3-chlorophenyl)-1,4-dihydropyridine, 7: A solution of 2,6-dibromomethyl-3,5-dicarboethoxy-6-methyl-4-(3-chlorophenyl)-1,4-dihydro-pyridine (obtained from 1.4 mmol of **1**) in THF (10 mL) was added dropwise to the solution of nucleophile $LiCHS(CH_2)_3S$[8] 4 mmol) in THF (30 mL, –78°C) during 1 h. After a few minutes, the cooling bath was removed and the temperature of the mixture was slowly (1 h) raised to 20°C and stirred at this temperature for 4 h, then evaporated. The residue was partitioned between CH_2Cl_2 and 2 M HCl, the organic layer washed with water, dried over Na_2SO_4 and evaporated. Purification of the crude product by preparative TLC (ethyl acetate/hexane 2 : 3) yielded **7** in 65% yield. m.p. 202–204°C; IR (KBr, cm^{-1}) $\bar{\nu}$: 3318, 3100, 2983, 1694, 1671, 1617, 1380, 1280, 1103, 785, ^1H NMR (400 MHz, $CDCl_3$) δ : 1.17–1.27 (m, 10H), 2.06–2.89 (m, 12H), 4.06–4.15 (m, 6H), 5.29 (m, 1H), 7.01–7.34 (m, 5H, ArH, N-H) ppm.

ACKNOWLEDGEMENT

Authors are thankful to Azarbaijan University of Tarbiat Moallem for financial support of this work.

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(*Received*: 15 January 2005; *Accepted*: 25 July 2005) AJC-4303